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First Total Synthesis of Optically Pure Deoxyschizandrin and Wuweizisu C. The Thermal Stability of Biaryl Configuration

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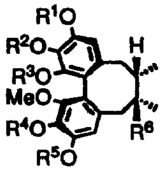
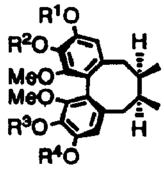
***Abstract:** The total synthesis of deoxyschizandrin (1) and wuweizisu C (2) having natural configuration was accomplished and the thermal stability of biaryl configuration was confirmed.*

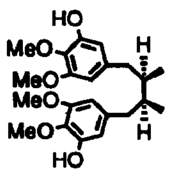
The fruits of *Schisandra chinensis* contain a large number of dibenzocyclooctane lignans, and the structures of which were elucidated by the extensive works of Ikeya and others.[1] Although these lignans possess common dibenzocyclooctane nucleus, they can be stereochemically classified into the following three subgroups depending on the configuration around the aryl-aryl bond, *i.e.*, (1) compounds with *R*-biaryl configuration (schizandrin (3),[1a,b] gomisin A (4),[1a] *etc.*), (2) compounds with *S*-biaryl configuration (wuweizisu C (2),[1c] gomisin N (5),[1d] *etc.*), and (3) compounds which occur as racemic mixtures (deoxyschizandrin (1),[1e] gomisin J (6),[1e] γ-schizandrin (7),[1f] gomisin M_1(8),[1f] *etc.*).



1: $R^1=R^2=R^3=R^4=R^5=Me$, $R^6=H$; (+)-deoxyschizandrin
3: $R^1=R^2=R^3=R^4=R^5=Me$, $R^6=OH$; (+)-schizandrin
4: R^1, $R^2=CH_2$, $R^3=R^4=R^5=Me$, $R^6=OH$; (+)-gomisin A
7: R^1, $R^2=CH_2$, $R^3=R^4=R^5=Me$, $R^6=H$; γ-schizandrin (racemic)
8: $R^1=R^2=Me$, $R^3=H$, R^4, $R^5=CH_2$, $R^6=H$; gomisin M_1 (racemic)

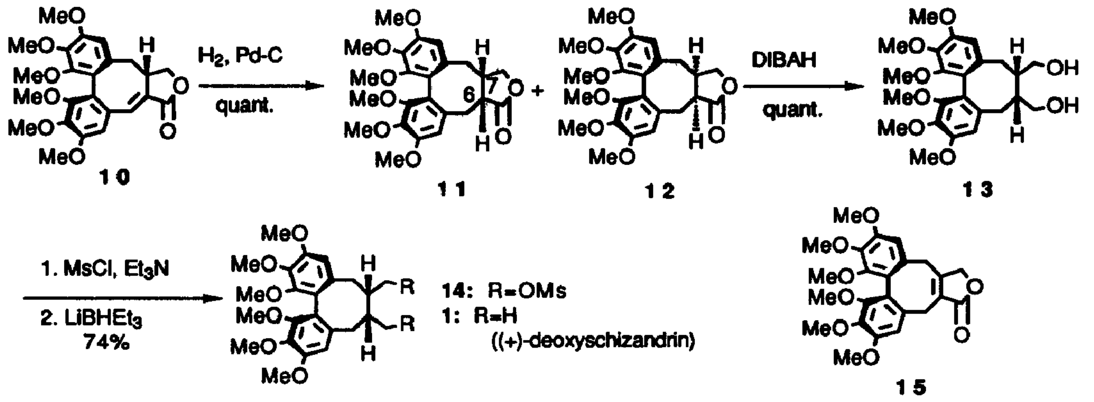


2: R^1, $R^2=CH_2$, R^3, $R^4=CH_2$; (-)-wuweizisu C
5: $R^1=R^2=Me$, R^3, $R^4=CH_2$; (-)-gomisin N
6: $R^1=R^4=H$, $R^2=R^3=Me$; (-)-gomisin J



9: pregomisin

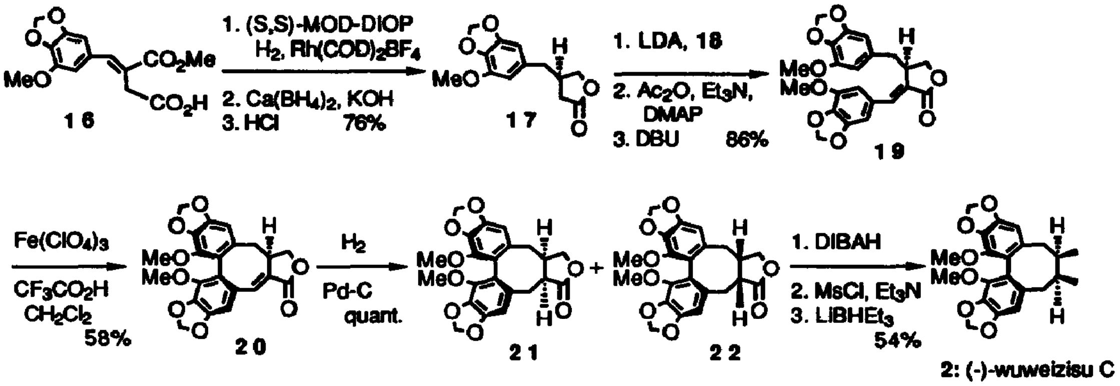
The occurrence of the both antipodes of ring systems in a plant arose the question how they were produced biosynthetically. Two possibilities could be derived from the consideration of the Ikeya's presumption that *meso*-dihydroguaiaretic acid and pregomisin (9) are the possible precursor of various oxygenated lignans in *Schisandra chinensis.*[1c] The first possibility is the low stereoselectivity in the step of oxidative coupling of pregomisin (9) to gomisin J (**6**). At the first stage of the biosynthesis, the non-stereoselective oxidative coupling to gomisin J took place and then each enantiomer was transformed into the corresponding natural products. The other possibility is the aryl-aryl bond rotation which resulted in the production of the racemic gomisin J irrespective of the stereoselectivity of the oxidative coupling of pregomisin. Although the second pathway seemed to be less plausible from the available knowledge about the configurational stability of biphenyl compounds,[2] the lack of the distinctive evidence could not eliminate this possibility. In this paper, we report the first total synthesis of optically pure deoxyschizandrin (**1**) and wuweizisu C (**2**) and exhibit the direct evidence for the configurational stability of **1** to eliminate the second possibility.[3]



Scheme 1. Total synthesis of optically pure (+)-deoxyschizandrin

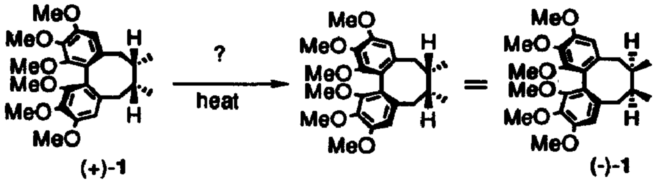
The synthesis of deoxyschizandrin was achieved starting from optically pure **10**[4] essentially according to the synthetic route to racemic deoxyschizandrin reported by Robin (Scheme 1).[3a] The catalytic hydrogenation of the double bond of **10** proceeded stereoselectively affording a mixture of **11** and **12**. The cis relationship between C(6) and C(7) position was confirmed by the fact that, on reduction of lactone moiety, both **11** and **12** gave a single diol (**13**). The formation of **12** is the result of palladium catalyzed isomerization of **10** to **15** and following hydrogenation of **15**.[5] Methanesulfonylation of **13** followed by the lithium triethylborohydride reduction afforded optically pure (+)-deoxyschizandrin (**1**). Deoxyschizandrin obtained in this manner showed good accordance with natural one with respect to the spectroscopic data (^{1}H-NMR, IR, MS), melting point, and optical rotation (synthetic (+)-**1**; mp. 114-115°C, $[\alpha]_D^{25}$ +108.2 (c=1.18, $CHCl_3$). natural (+)-**1**; mp. 116-117°C[1b], $[\alpha]_D$ +107 (c=5.7, $CHCl_3$)[1b]).

The synthesis of wuweizisu C (**2**) was achieved in the identical fashion starting from optically pure lactone (**17**), the antipode of the starting material for the synthesis of gomisin A (Scheme 2).[4] Aldol condensation of **17** with 3-methoxy-4,5-methylenedioxybenzaldehyde (**18**) followed by the oxidative coupling with iron perchlorate[7] gave desired biphenyl lactone (**20**) in good yield as an only isolable product. The preferred regioselectivity of the coupling reaction observed here is in good accord with the previous results.[4,7] Catalytic hydrogenation of **20** and following transformations described above afforded wuweizisu C (**2**) without any difficulty. The identity of the synthetic **2** with natural one was confirmed by the comparison of their spectroscopic data (^{1}H-NMR, IR, MS), melting points, and optical rotations (synthetic (-)-**2**; mp. 115-117°C, $[\alpha]_D^{28}$ -59.2 (c=0.6, $CHCl_3$). natural (-)-**2**; mp. 121-123°C,[1c] $[\alpha]_D^{22}$ -58.8 (c=1.02, $CHCl_3$)[1c]).



Scheme 2. Total synthesis of optically pure (-)-wuweizisu C

Next, we examined the thermal stability of the configuration of aryl-aryl bond of 1, the representative of gomisi lignans. As illustrated in Scheme 3, if the aryl-aryl bond rotation took place, the decrease of the optical purity of the compound should be observed because (+)-deoxyschizandrin would be transformed into (-)-deoxyschizandrin by the rotation. The examination was performed as follows. The optically pure (+)-deoxyschizandrin was heated at 200°C for 2 hours, and then, the optical purity of the recovered deoxyschizandrin was determined by using chiral HPLC method.[8] The results were shown in Figure 1. The HPLC analysis of the racemic deoxyschizandrin showed peaks at 40.6 min and 53.8 min (Figure 1, right), while the optically pure (+)-deoxyschizandrin at 54.8 min (Figure 1, left) suggesting that the peak at 40.6 min correspond to that of (-)-deoxyschizandrin. The HPLC analysis data of the thermally treated optically pure (+)-deoxyschizandrin was shown in the center of Figure 1. The chromatogram apparently showed the complete absence of the peak at 40.6 min, *i.e.*, the absence of (-)-deoxyschizandrin suggesting that *the anticipated aryl-aryl bond rotation did not take place*. Consequently, we concluded that the dibenzocyclooctane ring systems of gomisi lignans are thermally stable and the occurrence of racemic mixture in nature must not be ascribed to the aryl-aryl bond rotation.



Scheme 3. Racemization of (+)-1 by the aryl-aryl bond rotation

In conclusion, the thermal stability of the configuration of biphenyl linkage in gomisi lignans were confirmed, and subsequently, the aryl-aryl bond rotation was eliminated from the possible biogenetic path for the production of both configurations of dibenzocylooctane nucleus. The occurrence of the both configurations in nature should be ascribed to the low stereoselectivity of the oxidative coupling of pregomisin to gomisin J in the plants (Scheme 4).

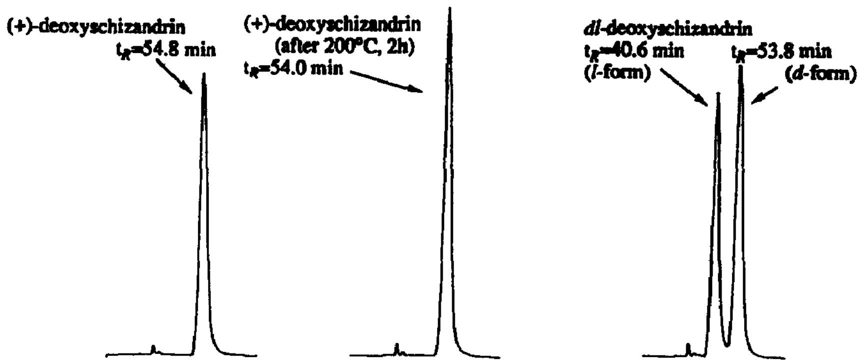
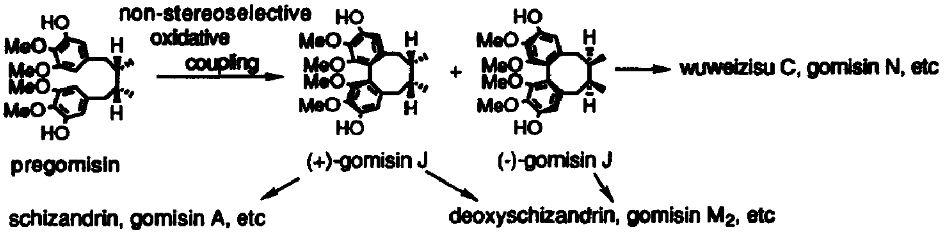


Figure. 1. HPLC charts of (+)-deoxyschizandrin, thermally treated (+)-deoxyschizandrin, and *dl*-deoxyschizandrin.[8]



Scheme 4. Elucidated biogenetic path of the gomisi lignans

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5. When the hydrogenation was carried out using aged palladium on carbon, the progress of the reaction terminated yielding **11** and **15**, see ref. 3a.
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8. HPLC analysis was performed with Daicel Chiral Cel OJ (4.6 mm x 25 cm) eluting with ethanol-hexane (2:98)(flow rate; 0.2 ml/min).

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